EFFICACY AND SAFETY OF EXPERIMENTAL CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELLS VERSUS AXICABTAGENE CILOLEUCEL (YESCARTA) FOR THE TREATMENT OF RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA: MATCHING ADJUSTED INDIRECT COMPARISONS AND SYSTEMATIC REVIEW

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Introduction: Despite the high response rates seen with Chimeric Antigen Receptor (CAR) T-cell therapy for relapsed/refractory Large B-cell lymphoma (R/R LBCL), post-therapy relapse remains a key challenge. To date, no study has evaluated the comparative efficacy and safety of experimental CAR T-cell products versus currently approved CAR T-cell therapies. **Objective:** To indirectly compare the efficacy and safety of novel, experimental CAR T-cell products against the first FDA-approved CAR T-cell construct, Axicabtagene ciloleucel (Yescarta). **Methods:** In compliance with the PRISMA guidelines, we performed a systematic review, which identified 16 independent, early-phase clinical trials consisting of 193 LBCL patients with individual patient data (IPD). We categorized eight pooled populations based on the target antigens (CD19, CD20), co-stimulatory domains (CD28, 4-1BB), and CAR T-cells administered with or without concomitant autologous stem cell transplant (ASCT). The pooled populations were categorized as follows: (1) dual targeting strategies, such as tandem CD19.CD20, n = 28; (2) co-infusion of CD19 and CD20 CARs, n = 21; (3) third-generation CARs, n = 26; (4) CD19 CARs with modified constructs for reduced toxicity, including CD19. BBz.86, n = 21; and (5) Hu19.CD828Z, n = 14; (6) CD19. 4-1BB.S manufactured in China, n = 24; (7) concomitant ASCT and CD19.CD28, n = 45; and (8) CD20 CARs with a 4-1BB co-stimulatory domain, n = 14. A Matching Adjusted Indirect Comparison (MAIC) statistical technique was applied to account for heterogeneity in the study population across trials. Estimates for the experimental CAR T-cell trials were adjusted using patient-level data to match the ZUMA-1 (Yescarta, n = 108) study population based on mutually reported key baseline covariates, including age, disease stage, histology, refractoriness, number of prior lines of therapy, and extranodal disease. The study endpoints for this study included progression-free survival (PFS), cytokine release syndrome (CRS), and neurotoxicity (NT). **Results:** In the dual-targeting strategy, only tandem CD19.CD20.4-1BB was associated with a statistically significantly improved PFS (HR = 0.46; 95% CI, 0.23-0.92) and a safer NT profile (OR = 0.15; 95% CI, 0.03-0.76) compared to Yescarta. As for safety, significantly reduced NT (OR = 0.19; 95% CI, 0.04-0.94) was also noted with third-generation CAR T-cells. None of the other comparisons were statistically significant. Of note, no statistically significant associations regarding PFS or safety were seen with the sequential administration of ASCT followed by CAR T-cells within 4-7 days. CD19. BBz.86 and Hu19. CD828Z CAR T-cell products containing modified co-stimulatory domains aimed at reduced toxicity demonstrated no grade ≥3 CRS nor NT occurrence. Anti-CD20.4-1BB did not show a remarkable difference in terms of the selected endpoints for this study. Safety data for the co-infusion of CD19 and CD20 were not available for this trial. **Discussion and conclusion:** Our MAIC suggests a dual targeting approach using tandem CD19. CD20.4-1BB might have both superior efficacy and safety compared to Yescarta. Future studies comparing experimental CAR T-cell constructs with other CD19. 4-1BB-based approved CAR T-cell products, such as Tisagenlecleucel (Kymriah) and Lisocabtagene maraleucel (Breyanzi), may further contribute to clarify these findings.

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ELABORAÇÃO DE UM LIVRO INFANTIL PARA CONVERSAR SOBRE TRANSPLANTE DE MEDULA ÓSSEA NA ANEMIA FALCIFORME

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Introdução: A Anemia Falciforme é uma doença genética pertencente ao grupo de doenças falciformes e caracteriza-se pela forma de maior gravidade clínica, sendo também a mais prevalente. O único tratamento com possibilidade curativa é o Transplante de Medula Óssea. Os autores do presente

trabalho elaboraram um livro em que a personagem Amanda, uma menina negra com Anemia Falciforme, ensinava sobre a doença para um colega de sala, Gabriel. O objetivo deste trabalho foi elaborar um livro, com os mesmos personagens deste primeiro, mas tendo como contexto Amanda no pós-transplante, com o intuito de auxiliar a criança e seus familiares a compreenderem as particularidades desse procedimento. **Método:** Foram seguidas as seguintes etapas: a) elaboração do projeto, b) seleção de conteúdos: realizado levantamento da literatura sobre Transplante de Medula Óssea para Anemia Falciforme; c) elaboração da história: escolha do cenário de isolamento pós-transplante e opção pela continuação do livro anterior; d) elaboração do livro piloto; e) revisão por especialistas: o material foi analisado por psicólogos e por uma médica com experiência no assunto; f) adequação da linguagem e conteúdos: foram realizadas as adaptações sugeridas; g) nova submissão do material aos especialistas; h) finalização do livro, que será ilustrado, catalogado e impresso. **Resultado:** A história é centralizada em um diálogo de Amanda com Gabriel no momento em que ela retorna para sua cidade natal, mas ainda necessita de cuidados especiais. Amanda vai contando para o colega todos os momentos vivenciados desde o pré-transplante, comentando da sua vivência e de seus sentimentos em cada período, bem como do que a ajudou a passar pelos momentos mais complicados. Os principais tópicos abordados na história foram: exames pré-transplante, mudança de cidade, escolha do doador, internação, classe hospitalar, implantação do cateter, início da quimioterapia e queda dos cabelos, infusão e pega da medula, equipe multidisciplinar, alta hospitalar, limitações pós-TMO, acompanhamento ambulatorial e ganhos percebidos da experiência. O livro encerra com orientações aos cuidadores das crianças e uma explicação mais aprofundada sobre a doença e o Transplante de Medula Óssea, pensando em pacientes mais velhos que possam vir a ter contato com o livro. **Conclusão:** O material produzido poderá ser utilizado em diversos contextos, como na saúde e na escola, informando crianças, pais, professores e profissionais da saúde de maneira lúdica e clara. Além do caráter educativo, o livro poderá ser usado como material intermediário facilitador para a expressão afetiva das crianças com Anemia Falciforme com indicação para o Transplante de Medula Óssea, que podem se identificar com a vivência da personagem Amanda. (Programa Unificado de Bolsas - USP).

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ENGRAFTMENT POTENTIAL OF CD34+ CELLS FROM SEVERE APLASTIC ANEMIA PATIENTS EXPANDED WITH UM171

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Objectives: Immune aplastic anemia (AA) is a hematological disease characterized by pancytopenia and bone marrow (BM) hypocellularity. It is caused by an immune attack against hematopoietic stem and progenitor cells (HSPC). Its treatment is based on allogeneic BM transplantation and immunosuppressive therapy. More recently, the addition of eltrombopag showed that the expansion of hematopoietic precursors is a therapeutic alternative. Fares et al. demonstrated that the small molecule UM171 is capable of expanding the most primitive $CD34^+$ cell compartment of umbilical cord blood (UCB) ex vivo. Our research group showed that UM171 is also capable of effectively expanding immature subpopulations of $CD34^+$ cells from patients with immune AA. The aim of this study was to evaluate the engraftment capacity of $CD34^+$ cells from patients with AA expanded with UM171 in a murine xenotransplantation model. **Methods:** $CD34^+$ cells were purified from either bone marrow of one patient or one UCB unit using immunomagnetic labeling with human CD34 MicroBeads, MS columns, and a magnetic separator. Cells were cultured for seven days in medium supplemented with cytokines and 35 nM UM171 or 0.1% DMSO (control) and then transplanted via retro-orbital injection into pre-conditioned 8-to-12-week-old female NSG-SGM3 (NSGS) mice. The progeny of 3×10^4UCB $CD34^+$ cells or 8.250 AA patient $CD34^+$ cells was transplanted per mouse (four mice per experimental condition). The conditioning regimen consisted of two intraperitoneal injections of 12.5 mg/kg busulfan administered 48 and 24 hours before transplantation. Human hematopoietic cells were monitored in the murine BM by flow cytometry at week 20 post-transplantation. BM cells were collected from the two femurs and the two tibias of each animal and treated twice with red cell lysis, labeled with APC-Cy7 anti-mouse and PerCP-Cy5.5 anti-human CD45 antibodies, then analyzed on a flow cytometer using the FlowJo V.10 software. **Results:** We found that both progenies of UCB and AA BM $CD34^+$ cells cultured with UM171 showed an improved reconstitution potential in mice BM 20 weeks after transplant compared to DMSO, which was demonstrated by the detection of higher percentages of human $CD45^+$ cells in the mice BM (UCB: UM171 = 10,07% ±2,29 vs DMSO = 3,73% ±1,99; AA BM: UM171 = 0,095% ±0,075 vs DMSO = 0,042% ±0,002; data represent mean ±Standard Error). Differences were not significant. **Discussion:** We wondered whether the UM171 treatment would impact the engraftment capacity of the in vitro expanded $CD34^+$ cells. The enhanced engraftment capacity enabled by UM171 could allow for immune AA patients to be treated with a novel strategy, autologous transplantation of their own $CD34^+$ expanded cells. The present study indicates that UM171 could be a promising candidate drug for treating patients with immune AA. More replicates (patients and controls) are required to firmly establish the benefit of UM171 in conferring repopulation potential to ex vivo expanded $CD34^+$ cells from AA patients. **Conclusion:** In initial experiments, in vitro treatment with UM171 appears to increase the engraftment of $CD34^+$ cells isolated from UCB and from the BM of immune AA patients. These results need to be confirmed in additional experiments.

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